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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/068,238
Filing Date: February 05, 2002
Appellant(s): BELL ET AL.

M. Angela Parsons
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed April 23, 2009 appealing from the Office action mailed January 24, 2008.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The following are the related appeals, interferences, and judicial proceedings known to the examiner which may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal:

Decision in the appeal No. 992550 (application No. 08/452,129) (Exhibit A).

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The amendment after final rejection filed on July 22, 2008 has been entered.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

1) Ramisse, V. et al. "Identification and characterization of Bacillus anthracis by multiplex PCR analysis of sequences on plasmids pXO1 and pXO2 and chromosomal DNA", FEMS Microbiology Letters, vol. 145, pp. 9-16 (1996).

2) Makino, S. et al. "Molecular Characterization and Protein Analysis of the cap Region, Which Is Essential for Encapsulation in Bacillus anthracis", J. Bacteriol., vol. 171, pp. 722-30 (1989).

3) Buck, G.A. et al. "Design Strategies and Performance of Custom DNA Sequencing Primers", BioTechniques, vol. 27, pp. 528-36 (1999).

4) Wittwer, C.T. et al., "Continuous Fluorescence Monitoring of Rapid Cycle DNA Amplification", BioTechniques, vol. 22, pp. 130-138 (1997).

5) Qi, Y. et al., "Utilization of the rpoB Gene as a Specific Chromosomal Marker for Real-Time PCR Detection of Bacillus anthracis", Appl. Env. Microbiol., vol. 67, pp. 3720-3727 (2001).

6) Price, L.B. et al., "Genetic Diversity in the Protective Antigen Gene of Bacillus anthracis", J. Bacteriol., vol. 181, pp. 2358-2362 (1999).

7) Bragg, T.S. et al., "Nucleotide sequence and analysis of the lethal factor gene (lef) from Bacillus anthracis", Gene, vol. 81, pp. 45-54 (1989).

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim interpretation

1. In view of the fact that claims 57, 70 and 83 do not state where the donor and acceptor are attached to, the claims are interpreted as having the two labels at any of the primers or probes.

2. In claims 67, 80 and 93, the limitation of a package insert having instructions for using primers and probes is not taken into account when comparing claims with the prior art, since the instructions (printed matter) do not constitute a structural limitation on primers or probes.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 57, 66 and 67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ramisse et al. (FEMS Microbiology Letters, vol. 145, pp. 9-16, 1996; cited in the IDS and in the previous office action), Makino et al. (J. Bacter., vol. 171, pp. 722-730, 1989; cited in the previous office action), Buck et al. (Biotechniques, vol. 27, pp. 528-536, 1999; cited in the previous office action), Wittwer et al. (Biotechniques, vol. 22, pp. 130-138, 1997; cited in the previous office action) and Qi et al. (Appl. Env. Microbiol., vol. 67, pp. 3720-3727, August 2001; cited in the previous office action).

A) Regarding claims 57, 66 and 67, Ramisse et al. teach primers for detection of capB gene (Table 2). The primers were designed by computer analysis using the Oligo primer analysis software (page 12, second paragraph). Ramisse et al. do not specifically teach oligonucleotides with SEQ ID NO: 1-4.

B) As can be seen from sequence alignments, SEQ ID NO: 1 is complementary to bp 371-389 of the cap gene of Makino et al., SEQ ID NO: 2 is complementary to bp 611-628 of the cap gene of Makino et al., SEQ ID NO: 3 is complementary to bp 523-554 of the cap gene of Makino et al., and SEQ ID NO: 4 is complementary to bp 556-585 of the cap gene of Makino et al., whereas the primers of Ramisse et al. are complementary to bp 1230-1249 and 2083-2102 of the cap gene (Table 2).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the method of Ramisse et al. with the use of functionally equivalent primers selected from the sequence of Makino et al., since Ramisse et al. expressly teach primer selection for B. anthracis detection using commercially available software from the B. anthracis published sequences and since Makino et al. provide such published sequences for the software program to analyze.

In the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologs, however, the Court stated,

> "Normally, a *prima facie* case of obviousness is based upon structural similiarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound

> may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties (see page 9, paragraph 4 of attached ref)."

Since the claimed primers simply represent structural homologs, which are derived from sequences suggested by the prior art as useful for primers and probes for the detection of B. anthracis, and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers and probes are *prima facie* obvious over the cited references in the absence of secondary considerations.

Buck et al. expressly provides evidence of the equivalence of primers. Specifically, Buck et al. invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck et al. also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18mer primers on the 300 base pair sequence (see page 530, column 1). When Buck et al. tested each of the primers selected by the methods of the different labs, Buck et al. found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck et al. expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck et al. provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

C) Ramisse et al., Makino et al. and Buck et al. do not specifically teach oligonucleotides comprising a donor fluorescent moiety and an acceptor fluorescent moiety.

D) Regarding claims 57 and 66, Wittwer et al. teach dual probes for detection of nucleic acids, with one part of the probe being labeled with a fluorescent donor and the other with a fluorescent acceptor (Fig. 1C; page 134, paragraphs 3 and 4; Fig. 4).

Regarding claims 57 and 66, Qi et al. teach real-time PCR detection of B. anthracis using two primers and two probes with sequences complementary to the rpoB gene. One probe is labeled with a fluorescent donor, fluoresceine, and the other with the fluorescent acceptor, Cy5 (Fig. 1; Table 3).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used fluorescent labeling of probes with donor and acceptor moieties of Wittwer et al. and Qi et al. in the B. anthracis detection probes of Ramisse et al., Makino et al. and Buck et al. The motivation to do so, provided by Wittwer et al., would have been that using dual probes allowed quantitation of low copy number of target nucleic acid (page 134, fourth paragraph; page 135, the end of first paragraph) and

"Fluorescence monitoring every cycle during DNA amplification is an extraordinarily powerful technique for quantification. With simple instrumentation and fluorescent monitoring each cycle, sequence-specific detection and quantification can be achieved in 5–20 min after temperature cycling has begun. Although the final fluorescence signal is decreased when low copy numbers are amplified, quantification between 0 and 1000 initial template copies appears possible (Figures 3 and 4). These techniques should be particularly useful in assays where rapid quantification is desired, such as in the amplification of clinical serum viruses." (page 138, last paragraph).

Further, the motivation to do so, provided by Qi et al., would have been that using FRET-based detection allowed detection of B. anthracis, a potential biological weapon, in less than an hour (Abstract), could detect as little as 1pg of DNA (page 3726, second paragraph), and "The FRET-PCR assay has several advantages over standard molecular identification techniques. The amplification is monitored in real time, and reactions can be scored as positive or negative without time-consuming routine gel analysis. Moreover, the assay is rapid and highly sensitive when extracted DNA is used as a template for PCR. … The presence of contaminating DNA does not affect the results of the assay, and hence it can be applied for detection of *B. anthracis* in epidemiological studies and suspected bioterrorist attacks and when analyzing ancient samples." (page 3726, last paragraph; page 3727, first paragraph).

6. Claims 70, 79 and 80 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ramisse et al. (FEMS Microbiology Letters, vol. 145, pp. 9-16, 1996; cited in the IDS and in the previous office action), Price et al. (J. Bacter., vol. 181, pp. 2358-2362, 1999; cited in the previous office action), Buck et al. (Biotechniques, vol. 27, pp. 528-536, 1999 ; cited in the previous office action), Wittwer et al. (Biotechniques, vol. 22, pp. 130-138, 1997; cited in the previous office action) and Qi et al. (Appl. Env. Microbiol., vol. 67, pp. 3720-3727, August 2001; cited in the previous office action).

Regarding claims 70, 79 and 80, Ramisse et al. teach primers for detection of pagA gene (Table 2). The primers were designed by computer analysis using the Oligo primer analysis software (page 12, second paragraph). Ramisse et al. do not specifically teach oligonucleotides with SEQ ID NO: 5-8.

B) As can be seen from sequence alignments, SEQ ID NO: 5 is complementary to bp 852-870 of the pagA gene of Price et al., SEQ ID NO: 6 is complementary to bp 1163-1180 of the pagA gene of Price et al., SEQ ID NO: 7 is complementary to bp 1041-1062 of the pagA gene of Price et al., and SEQ ID NO: 4 is complementary to bp 1064-1086 of the pagA gene of Price et al., whereas the primers of Ramisse et al. are complementary to bp 1925-1944, 2652-2671, 2006-2027 and 2135-2156 of the pagA gene (Table 2). Further, Price et al. teach primers for amplification of pagA gene (Table 1), which were designed from published pag sequence (page 2358, sixth paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the method of Ramisse et al. with the use of functionally equivalent primers selected from the sequence of Price et al., since Ramisse et al. expressly teach primer selection using commercially available software for B. anthracis detection from the B. anthracis published sequences and since Price et al. provide such published sequences for the software program to analyze, and also teach primers for amplification of pagA.

In the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologs, however, the Court stated,

> "Normally, a *prima facie* case of obviousness is based upon structural similiarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties (see page 9, paragraph 4 of attached ref)."

Since the claimed primers simply represent structural homologs, which are derived from sequences suggested by the prior art as useful for primers and probes for the detection of B. anthracis, and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers and probes are *prima facie* obvious over the cited references in the absence of secondary considerations.

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C) Ramisse et al., Price et al. and Buck et al. do not specifically teach oligonucleotides comprising a donor fluorescent moiety and an acceptor fluorescent moiety.

D) Regarding claims 70 and 79, Wittwer et al. teach dual probes for detection of nucleic acids, with one part of the probe being labeled with a fluorescent donor and the other with a fluorescent acceptor (Fig. 1C; page 134, paragraphs 3 and 4; Fig. 4).

Regarding claims 70 and 79, Qi et al. teach real-time PCR detection of B. anthracis using two primers and two probes with sequences complementary to the rpoB gene. One probe is labeled with a fluorescent donor, fluorescein, and the other with the fluorescent acceptor, Cy5 (Fig. 1; Table 3).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used fluorescent labeling of probes with donor and acceptor moieties of Wittwer et al. and Qi et al. in the B. anthracis detection probes of Ramisse et al., Price et al. and Buck et al. The motivation to do so, provided by Wittwer et al., would have been that using dual probes allowed quantitation of low copy number of target nucleic acid (page 134, fourth paragraph; page 135, the end of first paragraph) and

"Fluorescence monitoring every cycle during DNA amplification is an extraordinarily powerful technique for quantification. With simple instrumentation and fluorescent monitoring each cycle, sequence-specific detection and quantification can be achieved in 5–20 min after temperature cycling has begun. Although the final fluorescence signal is decreased when low copy numbers are amplified, quantification between 0 and 1000 initial template copies appears possible (Figures 3 and 4). These techniques should be particularly useful in assays where rapid quantification is desired, such as in the amplification of clinical serum viruses." (page 138, last paragraph).

Further, the motivation to do so, provided by Qi et al., would have been that using FRET-based detection allowed detection of B. anthracis, a potential biological weapon, in less than an hour (Abstract), could detect as little as 1pg of DNA (page 3726, second paragraph), and "The FRET-PCR assay has several advantages over standard molecular identification techniques. The amplification is monitored in real time, and reactions can be scored as positive or negative without time-consuming routine gel analysis. Moreover, the assay is rapid and highly sensitive when extracted DNA is used as a template for PCR. … The presence of contaminating DNA does not affect the results of the assay, and hence it can be applied for detection of *B. anthracis* in epidemiological studies and suspected bioterrorist attacks and when analyzing ancient samples." (page 3726, last paragraph; page 3727, first paragraph).

7. Claims 83, 92 and 93 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ramisse et al. (FEMS Microbiology Letters, vol. 145, pp. 9-16, 1996; cited in the IDS and in the previous office action), Bragg et al. (Gene, vol. 81, pp. 45-54, 1989; cited in the previous office action), Buck et al. (Biotechniques, vol. 27, pp. 528-536, 1999; cited in the previous office action), Wittwer et al. (Biotechniques, vol. 22, pp. 130-138, 1997 ; cited in the previous office action) and Qi et al. (Appl. Env. Microbiol., vol. 67, pp. 3720-3727, August 2001; cited in the previous office action).

A) Regarding claims 83, 92 and 93, Ramisse et al. teach primers for detection of lef gene (Table 2). The primers have lengths ranging from 15 to 24 bp. The primers were designed by computer analysis using the Oligo primer analysis software (page 12, second paragraph). Ramisse et al. do not specifically teach oligonucleotides with SEQ ID NO: 9-12.

B) As can be seen from sequence alignments, SEQ ID NO: 9 is complementary to bp 2469-2488 of the lef gene of Bragg et al., SEQ ID NO: 10 is complementary to bp 2791-2807 of the lef gene of Bragg et al., SEQ ID NO: 11 is complementary to bp 2607-2628 of the lef gene of Bragg et al., and SEQ ID NO: 12 is complementary to bp 2631-2652 of the lef gene of Bragg et al., whereas the primers of Ramisse et al. are complementary to bp 949-970, 1921-1941, 1238-1258 and 1599-1622 of the lef gene (Table 2). Further, Bragg et al. teach primers for sequencing of lef gene, which span the entire sequence of the gene (page 46, sixth paragraph; Fig. 1).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the method of Ramisse et al. with the use of functionally equivalent primers selected from the sequence of Bragg et al., since Ramisse et al. expressly teach primer selection using commercially available software for B. anthracis detection from the B. anthracis published sequences and since Bragg et al. provide such published sequences for the software program to analyze. Further, Bragg et al. teach primers spanning the entire sequence of the lef gene.

In the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologs, however, the Court stated,

> "Normally, a *prima facie* case of obviousness is based upon structural similiarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties (see page 9, paragraph 4 of attached ref)."

Since the claimed primers simply represent structural homologs, which are derived from sequences suggested by the prior art as useful for primers and probes for the detection of B. anthracis, and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers and probes are *prima facie* obvious over the cited references in the absence of secondary considerations.

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C) Ramisse et al., Bragg et al. and Buck et al. do not specifically teach oligonucleotides comprising a donor fluorescent moiety and an acceptor fluorescent moiety.

B) Regarding claims 83 and 92, Wittwer et al. teach dual probes for detection of nucleic acids, with one part of the probe being labeled with a fluorescent donor and the other with a fluorescent acceptor (Fig. 1C; page 134, paragraphs 3 and 4; Fig. 4).

Regarding claims 83 and 92, Qi et al. teach real-time PCR detection of B. anthracis using two primers and two probes with sequences complementary to the rpoB gene. One probe is labeled with a fluorescent donor, fluorescein, and the other with the fluorescent acceptor, Cy5 (Fig. 1; Table 3).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used fluorescent labeling of probes with donor and acceptor moieties of Wittwer et al. and Qi et al. in the B. anthracis detection probes of Ramisse et al., Bragg et al. and Buck et al. The motivation to do so, provided by Wittwer et al., would have been that using dual probes allowed quantitation of low copy number of target nucleic acid (page 134, fourth paragraph; page 135, the end of first paragraph) and

"Fluorescence monitoring every cycle during DNA amplification is an extraordinarily powerful technique for quantification. With simple instrumentation and fluorescent monitoring each cycle, sequence-specific detection and quantification can be achieved in 5–20 min after temperature cycling has begun. Although the final fluorescence signal is decreased when low copy numbers are amplified, quantification between 0 and 1000 initial template copies appears possible (Figures 3 and 4). These techniques should be particularly useful in assays where rapid quantification is desired, such as in the amplification of clinical serum viruses." (page 138, last paragraph).

Further, the motivation to do so, provided by Qi et al., would have been that using FRET-based detection allowed detection of B. anthracis, a potential biological weapon, in less than an hour (Abstract), could detect as little as 1pg of DNA (page 3726, second paragraph), and "The FRET-PCR assay has several advantages over standard molecular identification techniques. The amplification is monitored in real time, and reactions can be scored as positive or negative without time-consuming routine gel analysis. Moreover, the assay is rapid and highly sensitive when extracted DNA is used as a template for PCR. … The presence of contaminating DNA does not affect the results of the assay, and hence it can be applied for detection of *B. anthracis* in epidemiological studies and suspected bioterrorist attacks and when analyzing ancient samples." (page 3726, last paragraph; page 3727, first paragraph).

8. Claim 96 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ramisse et al. (FEMS Microbiology Letters, vol. 145, pp. 9-16, 1996; cited in the IDS and in the previous office action), Makino et al. (J. Bacter., vol. 171, pp. 722-730, 1989; cited in the previous office action), Price et al. (J. Bacter., vol. 181, pp. 2358-2362, 1999; cited in the previous office action), Bragg et al. (Gene, vol. 81, pp. 45-54, 1989; cited in the previous office action) and Buck et al. (Biotechniques, vol. 27, pp. 528-536, 1999 ; cited in the previous office action).

A) Regarding claim 96, Ramisse et al. teach primers for detection of capB gene, pag A gene and lef gene (Table 2). The primers were designed by computer analysis using the Oligo primer analysis software (page 12, second paragraph). Ramisse et al. do not specifically teach oligonucleotides with SEQ ID NO: 1-12.

B) As can be seen from sequence alignments, SEQ ID NO: 1 is complementary to bp 371-389 of the cap gene of Makino et al., SEQ ID NO: 2 is complementary to bp 611-628 of the

cap gene of Makino et al., SEQ ID NO: 3 is complementary to bp 523-554 of the cap gene of Makino et al., and SEQ ID NO: 4 is complementary to bp 556-585 of the cap gene of Makino et al., whereas the primers of Ramisse et al. are complementary to bp 1230-1249 and 2083-2102 of the cap gene (Table 2).

C) As can be seen from sequence alignments, SEQ ID NO: 5 is complementary to bp 852-870 of the pagA gene of Price et al., SEQ ID NO: 6 is complementary to bp 1163-1180 of the pagA gene of Price et al., SEQ ID NO: 7 is complementary to bp 1041-1062 of the pagA gene of Price et al., and SEQ ID NO: 4 is complementary to bp 1064-1086 of the pagA gene of Price et al., whereas the primers of Ramisse et al. are complementary to bp 1925-1944, 2652-2671, 2006-2027 and 2135-2156 of the pagA gene (Table 2). Further, Price et al. teach primers for amplification of pagA gene (Table 1), which were designed from published pagA sequence (page 2358, sixth paragraph).

D) As can be seen from sequence alignments, SEQ ID NO: 9 is complementary to bp 2469-2488 of the lef gene of Bragg et al., SEQ ID NO: 10 is complementary to bp 2791-2807 of the lef gene of Bragg et al., SEQ ID NO: 11 is complementary to bp 2607-2628 of the lef gene of Bragg et al., and SEQ ID NO: 12 is complementary to bp 2631-2652 of the lef gene of Bragg et al., whereas the primers of Ramisse et al. are complementary to bp 949-970, 1921-1941, 1238-1258 and 1599-1622 of the lef gene (Table 2). Further, Bragg et al. teach primers for sequencing of lef gene spanning the entire length of the gene (page 46, sixth paragraph; Fig. 1).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the method of Ramisse et al. with the use of functionally equivalent primers selected from the sequences of Makino et al., Price et al. and Bragg et al.,

since Ramisse et al. expressly teach primer selection using commercially available software for B. anthracis detection from the B. anthracis published sequences and since Makino et al., Price et al. and Bragg et al. provide such published sequences for the software program to analyze.

In the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologs, however, the Court stated,

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Since the claimed primers simply represent structural homologs, which are derived from sequences suggested by the prior art as useful for primers and probes for the detection of B. anthracis, and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers and probes are *prima facie* obvious over the cited references in the absence of secondary considerations.

Buck et al. expressly provides evidence of the equivalence of primers. Specifically, Buck et al. invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck et al. also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18mer primers on the 300 base pair sequence (see page 530, column 1). When Buck et al. tested each of the primers selected by the methods of the different labs, Buck et al. found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL

PRIMER functioned as well (see page 533, column 1). Buck et al. expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck et al. provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

(10) Response to Argument

Issues addressed by Appellant

I. Are claims 57, 66, 67, 70, 79, 80, 83, 92 and 93 obvious over Ramisse et al., Makino et al., Buck et al., Wittwer et al. and Qi et al. (claims 57, 66, 67), Ramisse et al., Price et al., Buck et al., Wittwer et al. and Qi et al. (claims 70, 79, 80) and Ramisse et al., Bragg et al., Buck et al., Wittwer et al. and Qi et al. (claims 83, 92 and 93), considering the following arguments:

A) Buck et al. teaches an automated sequencing reaction which is significantly different than a PCR amplification reaction, which uses at least two oligonucleotides, or a real-time PCR, in which four oligonucleotides are used, therefore primer design for real-time amplification is not always predictable. In support of this argument Appellant submitted the references of Elnifro et al., Tichopad et al., Abd-Elsalam, all of which deal with primer design in general, a reference of Csordas et al., which deals with selection of primers for detection of Salmonella enterica by real-time PCR.

B) In view of KSR v. Teleflex, the "known options" in the art are not "finite, identified and predictable".

C) In re Deuel is not relevant to the instant claims since the case dealt with the obviousness of nucleic acid sequences over references which disclosed an amino acid sequence, therefore In re Deuel does not indicate that a primer or probe sequence complementary to the target is a structural homolog.

D) Claimed primers and probes are not obvious over the cited references as supported by In re Bell.

E) The primer and probe sequences of SEQ ID NO: 1-4 (or 5-8, or 9-12) are not obvious because their combination leads to high sensitivity and specificity towards their targets, as shown in Examples 1-4. Appellant further argue that each of the probes (SEQ ID NO: 3, 4, 7, 8, 11 and 12) has a particular melting temperature which can be used to confirm the presence of B. anthracis in the sample.

Regarding A), sequencing, PCR amplification and real-time PCR are the same process which may differ in the number of primers involved. All three processes require the same fundamental steps: design and synthesis of primers, annealing of primers to a selected sequence and extension of the 3' ends of the primers by a polymerase. Appellant argues that sequencing uses only one primer, however, this is not true, since usually both DNA strands are sequenced to avoid errors. Further, for very long sequences of more than 1000 bp, more than one sequencing primer is used. Therefore, both sequencing and PCR require at least two primers, one for each strand of the DNA. Further, even though real-time PCR may require three or four oligonucleotides (one or two of them serving as a probe), only two of them are primers, while the

other serve as probes binding to the amplified fragments. Therefore, sequencing, PCR amplification and real-time PCR use two primers in a process governed by the same principles. In conclusion, selection of primers for sequencing is not qualitatively different from the selection of primers for PCR amplification or real-time PCR. Finally, Buck et al. provides evidence that 95 18 bp primers selected from a sequence of 300 bp at 3 bp intervals all perform as specific primers, and thus Buck et al. provides EVIDENCE of the equivalence of primers in extension type assays, which include PCR. Appellant's arguments cannot rebut this evidentiary showing.

The references provided by Appellant do not provide evidence that Appellant's primer selection was in any way unique. The references of Elnifro et al., Tichopad et al. and Abd-Elsalam all deal with primer design in general, and contain information well known to one of skill in the art how to select primers. The reference of Csordas et al., which deals with selection of primers for detection of Salmonella enterica by real-time PCR, is pertinent to this case in that even though previously known primer sets were found by Csordas et al. to be somewhat deficient when used in real-time PCR, a primer set designed using automated software based on the known gene sequence performed as expected, with high sensitivity and specificity (see page 189, fourth paragraph; page 191, paragraphs 5-9). Therefore, Csordas et al. actually provide evidence that primer selection using automated software results in selection of sensitive and specific primers, further supporting the expectation of success of designing primers based on a known sequence using software programs, as routinely used in the art.

Appellant's own evidence in form of Example 1, first paragraph, shows that the only step undertaken in primer and probe design was analysis of sequences using primer design OLIGO software from Molecular Biology Insights, Inc. (Cascade, OR). There is no evidence in

Appellant's disclosure that any of the primers selected were additionally tested before being used in the amplification reactions. Therefore, in "designing" the claimed primers and probes Appellant basically followed directions provided by an output of the primer design software, which is not an inventive process. As Ramisse et al. teach selection of their primers from the same gene sequences using primer design software Oligo from MedProbes (Oslo, Norway), their primers would most likely function in real-time PCR as well. Finally, the limitation that the primers be used for real-time PCR is not present in the claims, and even if it were, it would still require evidence that these primers were specifically selected for this purpose and that other primers selected from the same gene sequences did not function under conditions of real-time PCR, and such evidence was not provided by Appellant.

Regarding B), the genus of nucleic acids represented by fragments of a given nucleic acid sequence is not very large. For example, the capB gene is about 1490 bp long. The number of 20 bp oligonucleotides derived from that sequence every base pair would be 1490-20 +1 =1471 oligonucleotides, which is not a huge genus. Using a primer design software would allow elimination of structurally unwanted primers, making the number much smaller. Further, even if several pairs of primers were to be tested to determine whether they worked in a particular amplification reaction, this is a routine experimentation process, not an inventive one.

Regarding C), it is not relevant what In re Deuel was about, since the Court's statement provided in the rejection refers to any structurally similar compounds. The fact that In re Duel does not specifically discuss primers or probes and target nucleic acids does not diminish the relevance of that statement. In fact, one would be hard pressed to find better examples of

structural homologs than primers and probes, which are parts of the same target nucleic acid molecule by virtue of being complementary to one of the strands of the molecule.

Regarding D), the case of In re Bell the issue was whether the presence of an amino acid sequence of a protein in prior art combined with knowledge of how to isolate genes would render the claimed nucleic acids obvious. Therefore, since translating an amino acid sequence into a nucleic acid results in many possible nucleic acids because of the codon degeneracy, the Court concluded that the nucleic acids would not have been obvious. However, the issue in the instant case is whether two different nucleic acid fragments selected from the same nucleic acid sequence would be equivalent in their function as primers, therefore In re Bell is irrelevant to the instant claims.

Regarding E), Appellant states in Examples 4 and 5 that of 32 B. anthracis isolates 28 were positive for all three target genes, and one was false negative for capB, and that the primers and probes selected by Appellant had no cross-reactivity with other bacterial species. However, primers and probes of Ramisse et al., selected from different parts of the same genes, exhibited the same properties (Table 1). All of the B. anthracis strains possessing the pXO1 plasmid were detected with the lef and pag primers, and all of the B. anthracis strains possessing the pXO2 plasmid were detected with the cap primers, and all of the pXO1/pXO2 strains were detected with all three primers. In addition, the cap, lef and pag primers did not exhibit cross reactivity with other Baccilus species or other bacterial species. Therefore, primers of Ramise et al. selected from other parts of the same genes as primers selected by Appellant possess the same properties of sensitivity and specificity. Finally, the particular melting temperatures of the probes are not limitations in the claims, and every primer or probe has a melting temperature

which is dependent on the solution composition and the primer or probe sequence, therefore a melting temperature is an inherent property of any primer or probe.

II. Is claim 96 obvious over Ramisse et al., Makino et al., Price et al., Bragg et al. and Buck et al., considering the following argument:

"Applicants fail to understand how a claim reciting twelve very specific primer and probe sequences to three different gene targets can be obvious over the cited art. As indicated herein, a combination of four claimed primer and probe sequences (i.e., combination of four different specific chemical species) is not obvious over the cited references, and certainly not the particular combination of *twelve* primer and probe sequences recited in claim 96."

The reasons were provided above. In summary, Ramisse et al. teach detection of B. Anthracis using primers and probes for the capB, pagA and lef genes, selected from the appropriate gene sequences using primer selection software. In view of the fact that the gene sequences were known, selecting a primer set alternative to the particular sets provided by Ramisse et al. would have been obvious provided availability of primer design software, which was also used by Appellant to design the claimed primers and probes. The expectation of success is provided by Buck et al. and by Appellant-provided reference of Csordas et al.

(11) Related Proceeding(s) Appendix

Copies of the court or Board decision(s) identified in the Related Appeals and Interferences section of this examiner's answer are provided herein.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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